

**IN THE US PATENT AND TRADEMARK OFFICE**

In re application of

***Ezio BOMBARDELLI***

Serial No. ***10/563,965***

Group Art Unit ***1614***

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Examiner: ***Qiuwen, Mi***

For: ***“COMBINATIONS OF VASOACTIVE AGENTS, THEIR USE IN THE PHARMACEUTICAL AND COSMETIC FIELD, AND FORMULATIONS CONTAINING THEM”***

**DECLARATION UNDER RULE 132**

I, Ezio Bombardelli, declare and state as follows

1. I am citizen of Italy, residing at Milan (Italy), Via Val di Sole.
2. I am inventor of the invention described and claimed in the above-identified patent application.
3. I received a degree in Biological Science from the University of Pavia in 1962. From 1962 to 1989 I was a researcher, then I held the position of Head of the Research Laboratory at the company “Inverni della Beffa S.p.A.” – Milan. Since 1986, I have been Scientific Director of INDENA S.p.A., Milan. I am the author of more than 80 scientific publications, most of which concern medicinal plant technology. I am the inventor or co-inventor in more than thirty patents all concerning medicinal plant derivatives. I am a member of the Italian Chemical Society, Fédération Internationale Pharmaceutique (F.I.P.), Gesellschaft für Arzneipflanzenforschung and Phytochemical Society of Europe.
4. The experimental activities reported hereafter have been carried out under my supervision and responsibility:

***Comparative test***

The following gel formulations have been prepared in accordance with the above-referenced patent application:

*Test composition (gel)*

|                                  |             |
|----------------------------------|-------------|
| Visnadin                         | 0.30 g      |
| or                               |             |
| Esculoside                       | 0.50 g      |
| and                              |             |
| Amentoflavone                    | 0.40 g      |
| <i>Centella asiatica</i> extract | 1.00 g      |
| Lecithin                         | 20.00 g     |
| Cholesterol                      | 0.50 g      |
| Ethanol                          | 8.00 g      |
| Butylhydroxy toluene             | 0.01 g      |
| Imidazolidine urea               | 0.30 g      |
| Hydroxypropyl-methylcellulose    | 2.00 g      |
| Water                            | qs 100.00 g |

The effect of the test compositions was evaluated in 12 women suffering from cellulite, aged between 20 and 36 and weighing  $68.6 \pm 2.5$  kg on average. For comparison, 4 groups of 12 women each were treated with a placebo and with six different formulations, respectively, each of them containing one of the active ingredients present in the test composition and the same excipients, according to the following scheme:

| Group       | Active ingredient | Concentration |
|-------------|-------------------|---------------|
| 1 (placebo) | -                 | -             |
| 2           | <i>Visnadin</i>   | 0.3%          |
| 3           | <i>Esculoside</i> | 0.5%          |

|                         |                                  |      |
|-------------------------|----------------------------------|------|
| 4                       | <i>Amentoflavone</i>             | 0.4% |
| 5                       | <i>Centella asiatica</i> extract | 1.0% |
| 6 (US Appl. 10/563,965) | <i>Visnadin</i>                  | 0.3% |
|                         | <i>Amentoflavone</i>             | 0.4% |
|                         | <i>Centella asiatica</i> extract | 1.0% |
| 7 (US Appl. 10/563,965) | <i>Esculoside</i>                | 0.5% |
|                         | <i>Amentoflavone</i>             | 0.4% |
|                         | <i>Centella asiatica</i> extract | 1.0% |

Each woman was treated topically on the thighs with 1g formulation twice a day for 30 consecutive days. On day 31, the skin macrorelief (“orange peel effect”) was measured with the “*profilometry on digital imaging of pinched thighs analysis*” according to Bertin C. et al. J. Cosmet. Sci., 52, 199-210, 2001. In addition, the thigh circumference was measured according to Gasbarro V. and Vettorello G. F. in Cosmetics and Toiletries, 107, 64-66, 1992.

The results reported in Tables 1 and 2 below show that the effect each test composition is higher than the sum of the effects of the placebo and of the formulations containing one single active ingredient.

**Table 1 – Effect of the tested formulations on profilometric analysis of thigh macrorelief (Rz)**

| Group | T <sub>0</sub> | T <sub>30</sub> |
|-------|----------------|-----------------|
| 1     | 6.28 ± 0.7     | 6.31 ± 0.7      |
| 2     | 6.22 ± 0.6     | 5.48 ± 0.5      |
| 3     | 5.99 ± 0.3     | 5.43 ± 0.4      |
| 4     | 6.30 ± 0.6     | 5.71 ± 0.6      |
| 5     | 6.25 ± 0.6     | 5.62 ± 0.6      |
| 6     | 6.24 ± 0.5     | 2.84 ± 0.4**    |
| 7     | 6.21 ± 0.4     | 2.28 ± 0.3**    |

Rz = roughness parameter

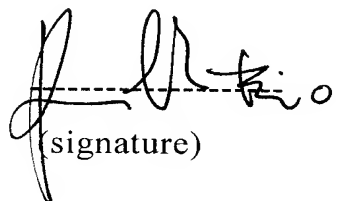
\*\* < 0.001 vs basal, Student's t test

**Table 2 – Effect of the tested formulations on left thigh circumference (cm)**

| Group | T <sub>0</sub> | T <sub>30</sub> |
|-------|----------------|-----------------|
| 1     | 54.8 ± 0.2     | 55.0 ± 0.2      |
| 2     | 54.7 ± 0.1     | 54.6 ± 0.1      |
| 3     | 57.23±0.2      | 57.10±0.1       |
| 4     | 55.1 ± 0.2     | 54.7 ± 0.1      |
| 5     | 54.9 ± 0.2     | 54.2 ± 0.1      |
| 6     | 54.6 ± 0.1     | 51.3 ± 0.1**    |
| 7     | 56.21 ± 0.21   | 53.10 ± 0.2**   |

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

6/21/2010  
(date)

  
(signature)